Management of gonococcal infection among adults and youth

New key recommendations

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Abstract

Objective To provide recommendations on the management of gonococcal infection among adults and youth.

Quality of evidence Treatment recommendations in the Canadian guidelines on sexually transmitted infections are based on review of the literature, as well as the grades of recommendations and the levels of evidence quality determined by a minimum of 2 reviewers. The recommendations are peer-reviewed and require approval by the expert working group.

Main message The new key recommendations for managing gonococcal infection among adults and youth include using culture as a diagnostic tool when practical, providing treatment with combination antibiotic therapy (ceftriaxone combined with azithromycin), and promptly reporting all cases with treatment failure to public health.

Conclusion Following these new key recommendations might reduce treatment failure, contribute to better surveillance of antibiotic-resistance trends in *Neisseria gonorrhoeae*, and contribute to the prevention of transmission of multidrug-resistant gonorrhea.

EDITOR'S KEY POINTS

- Long-term sequelae of untreated gonococcal infection can be serious for both the male and the female population. Of further importance is the emergence of gonococcal infection with resistance to antibiotics (including to cephalosporins), which has increased the possibility of treatment failure.
- Combination antibiotic therapy is recommended for treatment of gonococcal infection; the choice of medications varies by population and site of infection. Combination antibiotic therapy provides treatment with different mechanisms of action and might reduce the possibility of treatment failure and the development of further antimicrobial resistance.
- Using cultures as a diagnostic tool, when practical, ensures patients have been treated with the appropriate antibiotics, and the results inform public health surveillance: positive test results are reported, as gonorrhea is a notifiable disease in Canada. The addition of susceptibility information allows for better monitoring of resistance trends.

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The reported incidence of infection caused by *Neisseria gonorrhoeae* has been increasing since 1997 in Canada.[1,2] In 2012, there were 12 561 reported cases, for an incidence of 36.2 cases per 100 000 persons. The highest incidence rates are found among adolescents and young adults: 20- to 24-year-old men, 20- to 24-year-old women, and 15- to 19-year-old adolescent girls (148.5, 153.0, and 141.3 cases per 100 000 in 2012, respectively).[2] Eighty cases were also reported among 10- to 14-year-olds, and there were fewer than 5 cases reported among children younger than age 10.[2] Since the 1990s, the incidence rate has increased most rapidly among men and women aged 20 to 24.[1,2]

Long-term sequelae of untreated gonococcal infection can be serious.[3-5] Among females, who are often asymptomatic, complications include pelvic inflammatory disease, infertility, ectopic pregnancy, chronic pelvic pain, oculo-urethro-synovial syndrome (reactive arthritis), and disseminated gonococcal infection. Untreated males might develop epididymoorchitis, oculo-urethro-synovial syndrome (reactive arthritis), disseminated gonococcal infection, and (rarely) infertility.

Of further importance is the development of gonococcal antibiotic resistance. Among the *N gonorrhoeae* samples submitted to the Public Health Agency of Canada's (PHAC's) National Microbiology Laboratory, there is documented resistance to penicillins, tetracyclines, quinolones, and macrolides (including azithromycin), as well as, more recently, reduced susceptibility to cephalosporins, which is increasing over time.[6-10] Data estimating the true

prevalence of antibiotic-resistant gonococcal infection are limited, in part, by the large proportion of infection that is asymptomatic and therefore never diagnosed, and the shift to the use of nucleic acid amplification testing (NAAT) in place of culture.[11] Commercially available NAAT permits rapid diagnosis of gonococcal infection and allows for testing of urine samples. However, unlike culture, it does not currently provide information on antibiotic susceptibilities. Accurate and timely information regarding resistance is critical for management of individual cases and for the development of guidelines because of the potential for treatment failures.

It is essential that family physicians be aware of the most current diagnosis and management recommendations for uncomplicated gonorrhea in youth and adults because incidence has increased and treatment failure resulting in poor health outcomes is a real risk. The primary purpose of this article is to support primary care physicians in best practices as they relate to the use of cultures, combination drug therapy, and follow-up testing.

Quality of evidence

The *Canadian Guidelines on Sexually Transmitted Infections*[12] are created by PHAC under the guidance of an expert working group, which includes experts and researchers from the fields of medicine, nursing, microbiology, pharmacology, and public health. Members volunteer their time as authors and reviewers to maintain updated, evidence-based recommendations for the prevention, diagnosis, treatment, and management of sexually transmitted infections in Canada.

Recommendations are based on review of the literature, assessment of the quality of evidence, development through an iterative process with the primary authors, and approval by the expert working group. **Table 1**[12] summarizes the 5 grades of recommendation, which include recommendations for treatment (grades A and B), no recommendation (grade C), recommendation against treatment (grade D), and insufficient evidence (grade I). **Table 2**[12] summarizes the quality of evidence levels, ranging from randomized controlled clinical trials (level 1) to expert opinion (level 3).

The recommendation for combination therapy is based on emerging evidence: at the time of recommendation development, evidence was in press or available at conferences.

Main message

A comprehensive public health approach to management of gonococcal infection includes diagnosis, treatment (**Table 3**[7,9,13-25]), follow-up (including management of treatment failure), prevention of reinfection, partner notification, and public health reporting. The *Canadian Guidelines on Sexually Transmitted Infections* can be accessed online for more detailed recommendations.[12]

Table 1. Grades of recommendations

GRADE	RECOMMENDATION
A	Strongly recommends that clinicians routinely provide the treatment to eligible patients. There is good evidence that the treatment improves important health outcomes and the benefits substantially outweigh the harms
B	Recommends that clinicians routinely provide the treatment to eligible patients. There is at least fair evidence that the treatment improves important health outcomes and the benefits outweigh the harms
C	There is no recommendation for or against routine provision of the treatment. There is at least fair evidence that the treatment can improve health outcomes but the balance of benefits and harms is too close to justify a general recommendation
D	Recommends against routinely providing the treatment to asymptomatic patients. There is at least fair evidence that the treatment is ineffective or that the harms outweigh the benefits
I	The evidence is insufficient to recommend for or against routinely providing the treatment. The evidence that the treatment is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined

Data from Public Health Agency of Canada.[12]

Table 2. Quality of evidence

LEVEL	QUALITY OF EVIDENCE
I	There is evidence from at least 1 properly conducted randomized controlled trial
II	There is evidence from at least 1 well designed clinical trial without randomization, from cohort or case-control analytic studies (preferably from more than 1 centre), from multiple time-series studies, or from dramatic results in uncontrolled experiments
III	The evidence is from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

Data from Public Health Agency of Canada.[12]

Diagnosis. Diagnosis of gonococcal infection requires obtaining appropriate specimens for testing by either NAAT or culture. In some situations it might be appropriate to obtain specimens for both NAAT and culture. Nucleic acid amplification testing has higher sensitivity and specificity than culture does, which can result in more cases identified.[26,27] Also, NAAT provides positive test results sooner after exposure than culture does; therefore, NAAT is the diagnostic method of choice if testing occurs within 48 hours of exposure. Despite these advantages, cultures are recommended for individuals at increased risk of having antibiotic-resistant infection, as well as for the surveillance of trends in antibiotic resistance.[28-30] Culture is particularly

Table 3. Recommended treatment of uncomplicated anogenital and pharyngeal infections in adults and youth (≥ 9 y of age)

PATIENT GROUP AND INFECTION SITE	PREFERRED TREATMENT (DOSE)	GRADE OF RECOMMENDATION AND QUALITY OF EVIDENCE	ALTERNATIVE TREATMENT* (DOSE)	GRADE OF RECOMMENDATION AND QUALITY OF EVIDENCE
Patients other than MSM				
• Anogenital	Ceftriaxone (250 mg IM, single dose) in combination with azithromycin† (1 g orally, single dose)	A, II[13]	Spectinomycin (2 g IM, single dose) in combination with azithromycin† (1 g orally, single dose)	B, III[14,15]
	Cefixime‡ (800 mg, single dose) in combination with azithromycin† (1 g orally, single dose)	B, II[13]	Azithromycin§ (2 g orally, single dose)	B, I[16-19]
• Pharyngeal	Ceftriaxone (250 mg IM, single dose) in combination with azithromycin† (1 g orally, single dose)	A, II[13]	Cefixime‡ (800 mg, single dose) in combination with azithromycin† (1 g orally, single dose)	B, II[13]
			Azithromycin§ (2 g orally, single dose)	B, I[16-19]
MSM				
• Anogenital	Ceftriaxone (250 mg IM, single dose) in combination with azithromycin† (1 g orally, single dose)	A, II[13]	Cefixime‡ (800 mg, single dose) in combination with azithromycin† (1 g orally, single dose)	B, II[13]
			Spectinomycin (2 g IM, single dose) in combination with azithromycin† (1 g orally, single dose)	B, III[14,15]
			Azithromycin§ (2 g orally, single dose)	B, I[16-19]
• Pharyngeal	Ceftriaxone (250 mg IM, single dose) in combination with azithromycin† (1 g orally, single dose)	A, II[13]	Cefixime‡ (800 mg, single dose) in combination with azithromycin† (1 g orally, single dose)	B, II[13]

IM—intramuscularly, MSM—men who have sex with men.

*Alternative treatments are intended for use in cases in which there is a contraindication to the preferred treatment.

†A 1-g oral dose of azithromycin is preferred over the alternative of a 100-mg oral dose of doxycycline twice daily for 7 d owing to considerable rates of tetracycline-resistant gonorrhea and concerns regarding compliance with a 7-d treatment regimen. Doxycycline is contraindicated in pregnant and breastfeeding women.

‡There is scientific evidence that 800 mg of cefixime is safe and effective in treating gonococcal infections.[7,20-24] Pharmacodynamic studies have shown that 800 mg of cefixime compared with 400 mg of cefixime increases the period when the free drug concentration exceeds the minimum inhibitory concentration. Therefore, 800 mg might be more effective than the previously recommended 400-mg dose at reducing the risk of gonococcal treatment failure in settings of reduced cephalosporin susceptibility.[7,9,25] If cefixime is not available, all cases should be treated with ceftriaxone.

§A single 2-g oral dose of azithromycin should only be considered as an alternate treatment option if there is a history of severe allergy to cephalosporins. It is important to recognize the risk of treatment failure when using azithromycin monotherapy for the treatment of gonorrhea. There are also considerable gastrointestinal side effects associated with high-dose azithromycin.

important and should be used for testing, when practical, among the following populations:

- men who have sex with men (MSM),
- survivors of sexual abuse or sexual assault,
- women with suspected pelvic inflammatory disease,
- those who acquired the infection in geographic areas (Canadian[6] and international) with high levels of antibiotic resistance, or
- those with suspected treatment failure.

Individuals with gonococcal infection are frequently co-infected with *Chlamydia trachomatis*; therefore, testing should always be performed for both infections.[31] Because of shared transmission routes, the following interventions should be offered: serologic testing for syphilis; HIV testing (if not known to be infected) and counseling; and vaccination for human papillomavirus, hepatitis B, and hepatitis A if indicated.[12,32,33]

Treatment. In response to increasing antimicrobial resistance, combination therapy is recommended for gonococcal infection. **Table 3**[7,9,13-25] presents treatment options; the choice of medications varies by population and site of infection.

- Among MSM, other adults, and youth (≥ 9 years of age), the first-line therapy for uncomplicated anogenital or pharyngeal infections is ceftriaxone (250 mg intramuscularly, single dose) combined with azithromycin (1 g orally, single dose).

- For uncomplicated anogenital infection among patients other than MSM, cefixime (800 mg orally, single dose) combined with azithromycin (1 g orally, single dose) is also considered a first-line therapy.

These options use antibiotics with 2 different mechanisms of action and might delay the emergence of further cephalosporin-resistant gonorrhea by providing an additive or synergistic therapeutic effect.[34,35] It is desirable to use directly observed therapy in a single dose. The recommended combination therapy also provides effective treatment of chlamydia.[31] If cefixime is not available, all cases should be treated with ceftriaxone.

Follow-up. The emergence of *N gonorrhoeae* with resistance to cephalosporins has created the potential for treatment failure. *Treatment failure* is defined as the presence of at least 1 of the following (found in an appropriate specimen and in the absence of sexual contact during the posttreatment period):

- intracellular Gram-negative diplococci on microscopy in specimens taken at least 72 hours after completion of treatment,
- positive culture results for *N gonorrhoeae* taken at least 72 hours after completion of treatment, or
- positive NAAT results collected at least 2 to 3 weeks after completion of treatment.

The recommended timing of follow-up to administer a test of cure varies by method of testing to reduce the occurrence of false-positive results: 3 to 7 days after completion of therapy for cultures, and 2 to 3 weeks posttreatment for NAAT.[36,37] Although it is ideal to obtain a test of cure in all infected patients, it is particularly important in certain cases, which are presented in **Box 1**.

Screening for new infection should be done routinely 6 months posttreatment.[38]

Prevention

Prevention of reinfection: Prevention of reinfection is a key component of the management of gonococcal infection. Patients should be advised to abstain from unprotected sex until at least 3 days following completion of treatment and until their symptoms and those of their current sexual contacts have resolved. They should also be counseled on the risk of reinfection and effective prevention practices including safer sexual practices.

Partner notification: Case finding and partner notification are critical strategies to control gonococcal infection. Physicians have an important role in identifying potential cases. Consideration for case finding should be given to all individuals who have had sexual contact with the index case within the previous 60 days, and treatment should be provided regardless of clinical findings and pending laboratory results.[39,40] The length of trace-back time should be increased if the partner's test results are negative for gonococcal infection or if there were no sexual partners during the preceding 60 days.

Public health reporting. In all provinces and territories, gonococcal infection is a reportable infection. Treatment failures should be promptly reported to the local public health unit, which can inform provincial and territorial public health departments and PHAC.

Conclusion

Despite the inconvenience of cultures relative to NAAT, cultures can yield a number of benefits. First, making antibiotic susceptibility information available ensures patients have been treated with an appropriate antibiotic. Second, cultures inform public health surveillance: positive test results are reported, as gonorrhea is a notifiable disease in Canada. The addition of susceptibility information allows for better monitoring of resistance trends. The National Microbiology Laboratory tracks and reports resistance trends for the purpose of informing clinical and public health practices.

The shift to combination drug therapy is the primary change for family physicians to be aware of in this update. A review of the evidence for the use of single-drug therapy[14-25,41-47] and expert opinion on emerging combination drug therapy[13] forms the basis of this recommendation. However, recent evidence on combination drug therapies from laboratory,[34,35,48] observational,[13,49] and randomized clinical trials[50] supports this shift. These studies show evidence of additive or synergistic effects resulting from combinations of ceftriaxone and azithromycin,[34,35] cefixime and azithromycin,[35] and spectinomycin and azithromycin.[34] In addition, observational studies

Box 1. Cases in which test of cure is important to obtain

It is important to obtain test of cure from patients if ...

- they have pharyngeal infection
- compliance with therapy is doubtful
- there was re-exposure to an untreated partner
- there is documented previous treatment failure
- they were treated with an antibiotic other than ceftriaxone or cefixime
- they were treated with quinolones in the absence of confirmed susceptibility
- antimicrobial resistance to the administered therapy is documented or suspected
- the case is linked to another case with documented antimicrobial resistance to the treatment given or is linked to a case with treatment failure when the patient was treated with the same antibiotic
- infection occurred during pregnancy
- *Neisseria gonorrhoeae* was isolated from a woman undergoing therapeutic abortion
- complicated gonococcal infection exists

suggest that single-drug therapy with an oral cephalosporin has a higher relative risk of treatment failure compared with the ceftriaxone-azithromycin combination, the cefixime-azithromycin combination, and ceftriaxone alone.[13] Time-to-treatment-failure analysis also suggests that the ceftriaxone-azithromycin combination is superior to ceftriaxone-doxycycline combinations at 30 and 90 days.[49] Most recently, a randomized controlled clinical trial found near 100% efficacy for gentamicin-azithromycin and gemifloxacin-azithromycin combinations when measured by microbiological cure at 10 to 17 days.[50]

Combination antibiotic therapy provides treatment of gonorrhea with different mechanisms of action, and also treats chlamydia (often found concomitantly). Combination therapy might reduce the possibility of treatment failure and the development of further antimicrobial resistance.

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Contributors
All authors contributed to the literature review and analysis, and to preparing the manuscript for submission.

Competing interests
None declared

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